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EP 0712631 A2 EP 0700678 A1 EP 0429248 A2
EP 0282405 A2 WO 88/06438 A1 US 5529785 A
US 4158707 A

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(54) Abstract Title
Homogeneous lipid compositions for drug delivery

(57) A substantially homogenous composition for human administration comprises a biologically active lipophilic compound dissolved in or associated with at least one micelle-forming lipid preferably a phospholipid or sphingomyelin. For example cyclosporin A is dissolved or dispersed in a mixture of phosphatidylchlorine (PC) and lyso-PC. The composition may be made by dissolving the lipid material in ethanol, adding the lipophilic compound to the ethanol and removing the ethanol, after which the composition may be formulated for human oral administration, preferably as a gelatin capsule.

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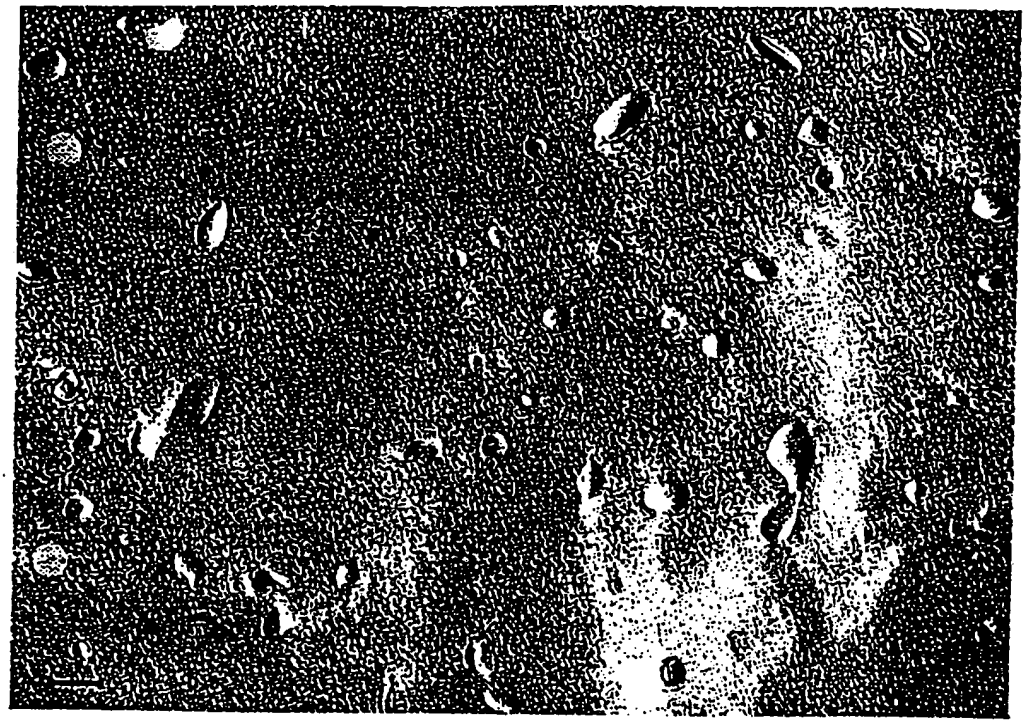

FIGURE 1

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PREPARATION OF PHARMACEUTICAL COMPOSITIONS

The present invention relates to the preparation of carriers for lipophilic materials in general. More specifically it relates to the formation of an improved carrier for these compounds which disperses in the presence of the aqueous contents of the gastro-intestinal tract (GI) to form drug-carrying lipid aggregates. The invention is particularly suitable for oral applications but can be readily adapted for other uses. The invention especially relates to novel phospholipid-cyclosporin formulations having improved bio-availability, increased efficacy and reduced toxicity and to a process of manufacture of such formulations.

Cyclosporins are fungal metabolites. They are hydrophobic neutral cyclic peptides and have essentially similar chemical and physical properties. Cyclosporin A (CyA) is representative and is the best known example. CyA is widely used in organ transplants to prevent rejection and as an immunosupressive agent in the treatment of systemic and local autoimmune disorders in which T cells play a major role. CyA has also been used to treat chronic conditions such as rheumatoid arthritis, asthma and non-malignant skin disorders. Derivatives of

CyA are also known to prevent multi-drug resistance from developing during treatment with cytotoxic drugs.

The clinical use of CyA in oral and intravenous dosage forms to prevent organ rejection was approved by the FDA in 1983. It has dramatically improved long-term survival rates in transplant patients. Most patients, however, still need to be maintained on life-long CyA therapy. This is normally provided in an oral form but may involve intravenous injection when it is necessary to obtain an adequate blood concentration quickly or oral therapy proves ineffective. Unfortunately, there are two major problems associated with oral therapy. Firstly, since the drug is lipophilic, its absorption from the GI tract is variable and incomplete, and bioavailability can range from 6% to 60%. This results in variable or inadequate blood concentrations which can bring about graft rejection and failure. Secondly, use of CyA is associated with nephrotoxicity. Impairment in kidney function is dose-related and increases with prolonged exposure, again emphasising the importance of controllable and predictable bioavailability.

There are few therapeutic compounds that have received more extensive and exhaustive pharmacodynamic and

pharmacokinetic examination than CyA. Investigations have shown that CyA has a narrow therapeutic index and that drug absorption takes place across an absorption window located along the upper part of the small intestine. Little absorption takes place in the stomach or colon.

The first CyA oral formulation introduced into clinical use (Sandimmune) comprised a solution of CyA dissolved in a solvent system of olive oil and ethanol (Patentschrift (Switz.) CH 641 356, 29 Feb. 1984, Appl. 79/1949. 27 Feb. 1979). The oil was emulsified in water using a polyethoxylated oleic glyceride surfactant to give a coarse O/W emulsion. This system was found to be inherently thermodynamically unstable. It is markedly affected by external conditions such as pH, temperature, diluting medium, surrounding medium and the presence of bile. As a result, drug tended to precipitate out of solution, and thus not be absorbed. The release of CyA from the oil-droplets and its subsequent absorption was also found to be highly dependent on the prevailing conditions in the GI tract e.g. composition of food and presence of bile and pancreatic enzymes. This formulation thus gave erratic inter- and intra-patient

bioavailability.

Although these problems were widely recognised, Sandimmune was relied upon exclusively by transplant patients for a number of years. It is only recently that a new oral formulation of CyA called Sandimmune-Neoral with improved pharmacokinetics has been introduced to address these problems. This formulation was introduced as a 'high-technology' microemulsion system in which the CyA is dissolved in a solvent consisting of a mixed lipophilic (corn oil mono-, di- and triglycerides) and hydrophilic (propylene glycol) solvent stabilised by an appropriate amount of a powerful surfactant, polyoxyl-40 hydrogenated castor oil (Kovarik et al, J. Pharm Sciences, 83, 444 (1994), and Hall, Inpharm, 10 December p 13 (1994)). This new formulation is reported to have self-emulsifying properties and immediately forms a transparent microemulsiuon in aqueous fluids. The CyA is dissolved in colloidal oil droplets (10-100nm diameter) stabilised by the surfactant and can be diluted without precipitation, having similar properties to a real aqueous solution.

Sandimmune-Neoral is at present the only known oral formulation generally available that gives consistent

absorption, independent of bile and food. Clearly, in view of the number of patients world-wide who need to be on long-term CyA maintainance and their individual circumstances , it would be most desirable for there to be a comparable bioequivalent formulation that does not rely on the presence of potentially harmful synthetic surfactants.

A number of alternative approaches to the solubilisation of CyA and the development of formulations that avoid the dual problems of variable bioavailabilty and incomplete absorption from the GI tract have been described in the prior art.

Polyvinyl pyrollidone (PVP) with molecular weights of 40,000 and 17,000, have been used as solubilising agent to carry the drug (Yonish-Rouach et al Journal of Immunological Methods 135, 147-153 (1990)). It was demonstrated that CyA can be solubilised and retain its activity (in vitro) in aqueous solutions of PVP. However, no evidence that the formulation would work in vivo was presented.

Co-administration of d-alphatocopheryl-polyethylene-glycol-1000 succinate (TPGS) which can form micelles has

been reported to lead to an improvement of CyA absorption in children after liver transplantation (Sokol et al., The Lancet 338, 212-215, (1991)).

In order to counter the poor solubility of CyA, Guzman et al., have immobilised the drug in nanoparticles of polymeric nanomatrix composed of either isobutyl-2-cyanoacrylate monomer or poly-E-caprolactone, in the presence of Pluronic F-68 (Journal of Pharmaceutical Sciences 82, 498-502 (1993)). However, the drug-free nanoparticles also exhibited immuno-supressive activity suggesting that they are unlikely to be a suitable vector for carrying CyA.

The enhancement of the intestinal absorption of a cyclosporine derivative (used as a model for CyA) by using milk fat globule membrane (MFGM) as an emulsifier of lipophilic cyclopeptides has been reported (Biol. Pharm. Bull. 17, 1526-1528(1994)).

In cases, where it is necessary to administer CyA intraveneously, it is normally formulated in an injectable form using a solvent consisting of ethanol and Cremophor EL., a tri-ricinoleate ester of ethoxylated castor oil. This solubiliser frequently gives rise to

anaphylatic reactions and is itself known to cause nephrotoxicity exacerbating problems associated with the inherent renal toxicity of CyA .

A well-recognised approach to the formulation of lipophilic drugs is liposome encapsulation in which the drug is intercalated into the lipid bilayer(s) of the liposome. Compositions, methods of preparation, applications, advantages and disadvantages of liposomes have all been extensively reported, and there are more than 30 publications describing liposomal entrapment of CyA mainly for possible intravenous and systemic use.

From purely pharmaceutical considerations, there is general consensus that liposome entrapment significantly reduces nephrotoxicity. However there is less certainty about whether the reduced nephrotoxicity reported with intravenous liposomal formulations is in fact due to altered pharmacokinetics of liposome encapsulated CyA or the non-specific, physical binding of the drug to other lipids present in the system.. Some reports claim that CyA pharmacokinetics depend on such factors as liposome charge, size and composition. Fahr (Pharmaceutical Research, 12, 1189-1198 (1995)) dismisses this idea and cites evidence suggesting that high lipid

doses tend to bind CyA in blood, thereby minimising the amount of drug available in sensitive organs like the kidney.

Apart from factors influencing the inherent nephrotoxicity of CyA, the three key factors in determining the suitability of carriers for CyA for oral and systemic use are: that the vector system should be non-toxic/irritant; it should have high entrapment levels and it should be stable. Membrane lipids are present in all living cells and represent a significant component of our diet and thus their use present no toxicity problems. There are, however, problems regarding entrapment levels and stability.

The charge, nature of the headgroups, and the saturation of the hydrocarbon chains have all been shown to influence the level of entrapment of CyA in liposomes. There is, however, consensus amongst those engaged in liposome work that the lipid:CyA molar ratio at equilibrium is about 19:1 for egg phosphatidylcholine. This should, however, be considered as a lower limit as in our own experience, unless the lipid:drug ratio is substantially greater than 20:1, the bound CyA in the liposome membrane will diffuse out into the surrounding

aqueous medium and will precipitate out as untrapped CyA crystals on standing.

This problem is not fully recognised and many of the earlier studies, particularly those in which drug entrapment is measured by the analysis of liposomal pellets obtained by ultracentrifugation and no account is taken of the proportion of non-entrapped drug, tend to cite unrealistically high entrapment values.

EP O 697 214 A1, describes aqueous compositions, with liposomes having a size less than 100 nm, prepared by homogenising a specific mixture of a phosphatidylcholine, phosphatidyl glycerol and cyclosporin in a mole ratio of from 25:3:1 to 17:3:1. The claims for particle size and drug entrapment would appear to render the compositions suitable for intravenous administration of CyA.

PCT Publication No: 90/00389 discloses a method for the preparation of freeze-dried compositions of CyA in liposomes. The liposomes are intended to be reconstituted immediately before use in an attempt to solve the problems of stability and crystal formation. It discloses lipid:drug ratios in the region of 20:1.

It is well known in formulation work that free CyA crystals are not absorbed from the GI tract resulting in poor bioavailability. In the case of intravenous injection, the formation of CyA crystals must be avoided at all costs. In practice, it is this crystallisation process that is the main reason why many liposome formulations perform so badly and do not proceed beyond animal testing.

Even if the formulations described in both the above disclosures have successfully managed to overcome these problems, they would still be exceedingly expensive to produce because of the lipids used, particularly at the high lipid/drug ratios involved, and the relatively complex production processes involved.

In general, technical problems relating to entrapment and stability combined with high production costs have, to date, limited the wider use of liposomes as carriers for drugs. Only amphotericin and doxorubicin are presently in clinical use. These products are for life-threatening conditions and the quantities used are relatively small to justify the high costs of the lipids and the complex manufacturing processes involved.

Apart from their use in liposomes, there is some report in the prior art describing the use of phospholipids for improving the dissolution of oil- soluble compounds or improving their absorption from the GI tract. The preparation of solid lipid-drug co-precipitates using diacyl phospholipids to increase the dissolution behaviour of poorly water-soluble drug solvates, and the possibility of modifying drug release from such dispersions by incorporation of small amounts of polymers, has been described (J. Pharm. Sci. 81, 282-286 (1992)). The amount of phospholipid employed, was much lower than the amount of drug and these preparations involved the incorporation of lipid in the crystalline structure of the drug solvate.

PCT/US86/00637 discloses the use of non-esterified fatty acids and monoglycerides in molar ratios between 1:2 and 2:1 together with up to 30 mole percent of a monacyl lipid, lyso-phosphatidylcholine (lyso-PC), to form lipid particles which show improved oral absorption when used as carriers for various lipophilic compounds.

Vehicles described as circulating micro-reservoirs, suitable for delivering xenobiotics are disclosed in USP 4,298,594. The compositions consist of diacyl

phospholipids together with sufficient cholesterol esters to render them more hydrophobic. They are claimed to give improved in vitro and in vivo stability to lipophilic drugs as well as enhanced oral absorption.

The object of the present invention is to provide a bulk lipid carrier, particularly for lipophilic compounds, that is safe, efficient and effective. All the existing carriers for lipophilic compounds are solvent systems based on combinations of hydrophilic, lipophilic and ethoxylated chemical surfactants. Although the carrying capacity may be adequate, these chemicals can be potentially harmful, particularly if administered in large amounts over a prolonged period.

Given the proven benefits of phospholipid-based preparations, it would be highly desirable to find a means to exploit their unique carrier potential without the practical limitations of presently available systems. The work reported in the prior art points to the need for an efficient, effective and non-toxic carrier for lipophilic compounds. Such needs are not unique to the cyclosporins. There are many biologically active compounds where optimum bioavailibilty cannot be expressed because of poor solubility. In some of the new

antifungal and cytotoxic compounds, activity is often linked with lipophilicity. Many lipophilic drug candidates do not progress to further human clinical evaluation because of a lack of a suitable formulation that would allow the potential benefits of the compound to be assessed. Therefore, a non-toxic carrier that transports lipophilic compounds in molecular dispersion would be of considerable benefit.

The present invention is based on the solubilisation of lipophilic drugs such as CyA in mixtures of diacyl lipids (for example PC) and monoacyl lipids (for exmaple lyso-PC), wherein PC means phosphotidyl choline. The reasons for the use of such mixtures is three-fold. Firstly, we find that such mixtures are capable of solubilising much higher amounts of CyA than diacyl lipids alone. The reasons for this are not clear but may reflect an association due to steric factors and/or membrane topography. Secondly, the presence of the monoacyl lipid appears to enhance the dispersability of these mixtures in aqueous media. Thirdly, the bioavailability of CyA is greatly improved. The reasons for this are again not fully clear but are probably related to the fact that PC and fat-soluble compounds such as CyA are absorbed in the same region of the gastro-intestinal tract.

The absorption, transport and pharmacokinetics of phospholipids are well-known. Over 90% of the diacyl lipid phosphotidylcholine (PC) entering the GI tract is absorbed from the upper region of the intestinal lumen where fat-soluble substances are also absorbed. Almost all of this PC is first hydrolysed to form (lyso-PC) monoacyl lipid. This, together with bile salts, monoacylglycerols and free fatty acids, then form mixed micelles within the lumen which are taken up by intestinal epitheleal cells. Fat-soluble materials such as CyA tend to partition into such micelles and be co-transported across the mucosal membrane. Whilst it is not suggested that the presence of phospholipids and lyso-phospholipids employed in the invention actively transport the associated compounds per se across intestinal mucosa, it is likely that absorption of lipids and lipid-soluble compounds take place in parallel. The increased presence of PC and lyso-PC are likely to improve the bioavailability of CyA.

In sharp contrast to the synthetic ethoxylated surfactants used in earlier formulations, PC and lyso-PC are endogenous compounds naturally present together in the intestinal mucosa and their presence is likely to be helpful rather than harmful. The mechanism of uptake of

CyA from the micelles formed by such detergents is not known but their strong detergency could potentially damage and alter permeability of the mucosa. This may, of course, be one reason why ethoxylayed surfactants are used as carriers to promote improved absorption.

Following transport into the epitheleal cells, the CyA enters the blood-stream where it probably partitions into the lipid components of the high and low density lipoproteins and the membranes of erythrocytes and other cells as hypothesised by Fahr (1995) in the case of direct intravenous injection.

The present invention is a carrier system that comprises an intimate mixture of conventional bilayer forming diacyl lipid(s), together with one or more monoacyl lipid, or other related micelle forming amphipath. On mixing with aqueous fluids, the carrier system is converted into lipidic particles which, depending on the chosen ratios of diacyl and monacyl lipids, may be in the form of liposomes, micelles or mixed micelles. At this stage, the lipophilic drug incorporated in the original carrier system may be present in a molecular form intercalated between the lipids making up the lipid particles or held in the form of a lipid-drug complex.

The molar ratio of diacyl lipid to monoacyl lipid, or other micelle forming amphipath, in the mixture may be from 1:99 to 99:1, preferably between 1:1 and 25:1. However, it may be possible to use lyso-PC alone in some circumstances.

Preferably, the diacyl lipid(s) chosen is a phospholipid. Examples of phospholipids are phosphatidylcholine, phosphatidylethanolamine, phosphatidylglycerol, phosphatidylinositol, phosphatidylserine and sphingomyelin. The acyl chain can either be unsaturated or saturated and can have between 12 to 22, preferably 14 to 18 carbon atoms. Other liposome forming membrane lipids such as glycolipids, ceramides, gangliosides and cerebrosides can be used in place of, or partial place of, phospholipids. The monoacyl lipid is preferably the monoacyl derivative of a phospholipid, but it can also be the corresponding monoacyl derivative of glyco lipids, sphingolipids, or any other suitable micelle forming lipid.

In practice, instead of mixing pure fractions of the lipids together to obtain the desired ratios, partially enzyme digested mixtures of lecithin that have the required proportions of the diacyl fraction to monoacyl,

can be used. These phospholipid mixtures, which are also classed as lecithins, are freely used in foods without restrictions and should thus provide no problems for oral use.

The monoacyl lipid content in formulations suitable for intravenous use are in the lower region of the preferred range. Lysolecithin has known haemolytic activity but mixtures of diacyl- and monacyl phospholipids in the molar ratio of 2:1 have been shown to be non-haemolytic at concentrations up to 1.3 mM in physiological saline. Some polyethoxylated surfactants, in contrast have been reported to produce 100% haemolysis in in vitro tests at concentrations as low as 0.2 mM (Pharm. J. 253, 463 (1994)). It should be borne in mind that although the possibility of haemolysis is an important issue in intravenous use when the injection is given as a bolus, it is much less so in cases of slow parenteral infusion. However, the use of lyso-PC is not of concern in oral applications as it is naturally present in the intestinal lumen.

The mass of lipophilic compound that is solubilised in the bilayer lipids can be anywhere between 1:1 to 1: 20 based on the molecular weight of compound to mono acyl

lipid. Preferably it is between 1:2 to 1: 10. The relative amount of the lipid mixture required for maximum entrapment will depend on various factors such as, type of lipid, charge, ratio of diacyl to monoacyl fractions and the solubility of the compound. Generally, an increase in the monoacyl fraction results in higher association with the compound and less total lipid will be required. Increased lipophilicity of the compound also improves lipid association. From practical and cost considerations, the least amount of lipid concomintant with achieving maximal solubilisation and bioavailability, should be employed. This should be readily achievable given the correct proportions of diacyl to monoacyl lipids.

It is preferred that the lipophilic compound is carried substantially in molecular form. The best method to achieve this is to dissolve the compound in a suitable solvent first. This solution is then used to solubilise the mixture of lipids. Depending on the lipids employed, a small amount of water, polyol or sugar, may be included to aid dispersion and solubilisation. Alternatively, the solution of drug is added to the lipid mixture dispersed or solubilised in a minimal amount of the same or a different solvent. A further method is to allow the

lipophilic compound to solubilise in the solution of lipids. This is a much slower process and may be accelerated by maintaining the mixture at an elevated temperature.

In practice, it is convenient to select a solvent that will solubilise or disperse both the lipid mixture and the compound to be carried. Where possible, ethanol is preferred, because it is considered non-toxic for pharmaceutical purposes. However other aliphatic alcohols such as methanol, isopropyl alcohol, propyl alcohol, butanols or volatile hydrocarbons, may be used. Other solvents such as chloroform, dichloromethane solvent, DMF, DMSO, etc, can also be used in some circumstances to facilitate molecular dispersion of the compound in the lipid, as long as they are carefully removed afterwards.

Following dissolution most if not all of the solvent is removed leaving behind a molecular dispersion of the compound in the lipid mixture. The solvent can be removed by simple rotary evaporation, evaporation under reduced pressure, evaporation on a drum at elevated temperature, spray drying or supercritical extraction. Spray drying and supercritical extraction would result in the

production of a fine powder formulation. The preferred method is simple evaporation under vacuum at slightly elevated temperature. Any suitable method can be employed to remove the solvent, provided that, given the correct mixture and proportion of lipids in the formulation, the compound remains substantially in molecular dispersion after removal of the solvent. In some cases, depending on the compound, it may be desirable to leave a small amount (1% to 5%) of ethanol or other hydrophilic medium, including water behind. The presence of a small amount of a hydrophilic medium could aid entrapment and could also modify the rheology of the composition to facilitate processing into appropriate dosage forms. The consistency of the final composition can be a fluid or viscous, paste-like material, or it could be a soft or hard wax, depending on the lipid composition and the inclusion of small amounts of 'excipients' to modify the rheology or consistency. It is essential that any such excipients should not adversely affect entrapment and performance.

A surprising discovery in this invention is the high solubilising capacity of the lipid mixture and the stability of the formulation. As mentioned, this can be a paste-like material in soft capsules, or if the

composition is a hard wax, it can be comminuted and filled into hard gelatine capsules. Alternatively, it could be dispersed in aqueous media to form a suspension, just before use. With careful selection of the bilayer lipi mixture and processing control, the invention could in certain circumstances be suitable for parenteral use after dilution. The unique features also enable it to have other novel uses, such as in inhalation and topical delivery.

Unlike liposome preparations, no external aqueous medium is necessary and therefore stability and microbial contamination should not be an issue. Furthermore, expensive and energy intensive equipment is not required to produce liposomes with well defined characteristics. Absence of intensive shearing forces involved in some methods of preparing liposome suspensions avoids the loss of entrapped compound. Thus the invention overcomes two major disadvantages in using liposomes as carriers, namely, physical instability of the vesicles and low entrapment. In addition, large scale production is easily undertaken. Although most compounds can be carried in the invention in so far as they are substantially in molecular dispersion, it is particularly suitable for carrying water-insoluble lipophilic compounds

particularly fungal metabolites (e.g. cyclosporin), and anti-fungal and cytotoxic compounds that give variable absorption and would otherwise have to be dissolved in organic solvents or chemical surfactants for administration.

A further unexpected feature of the invention is that the compositions described will readily disperse into discrete microscopic/colloidal lipid aggregates in the presence of an aqueous fluid, even at room temperature, with minimum agitation. The lipid aggregates obtained on dilution are uniform and mostly in the region of 100 nm. Lipophilic compounds remain in association within the aggregates. Depending on the combination of diacyl- to monoacyl lipids and their configuration, the aggregates may be vesicular or non-vesicular. They may be bilayer in form, complexes of bilayers and micelles, or totally micellar. Given the appropriate lipid mixture, the size of the lipid aggregates is unaffected on dispersion in aqueous fluid between the physiological pH range i.e. 2 to 8. The monoacyl components both promote solubilisation in the lipid mixture and also aid dispersion into small aggregates in the presence of aqueous medium. Bile salts and other emulsifiers are not essential for release of the compound for absorption

in the GI tract as the compound is largely in molecular dispersion in the lipid. However, as a bonus, dispersion into lipid aggregates should be further improved in the presence of emusifiers such as bile salts particularly at 37°C.

The present invention can be used to carry different types of compounds for various applications, but it is particularly suitable for carrying lipophilic compounds, especially for oral administration. By way of example, and not by way of limitation, the following examples are disclosed, where the compound being carried is CyA. However, it must be understood that these formulations are not limited to the examples shown. Other lipophilic compounds can be substituted into the type of formulations shown in the examples below, by those skilled in the art, by selecting the appropriate quantity of lipids, ratio of diacyl to monoacyl fractions and cognisant of physical properties of the lipid, such as charge, chain length, degree of saturation and phase transition temperature. The solvent used and the presence of residual hydrophilic medium left in the bulk lipid carrier should also be taken into account, as they could affect the association of the compound.

The invention is illustrated in the following examples.

Example 1.

100 g of PC, lyso-PC, CyA (M. Wt 1202) in the molar ratios 10:7:1 was added to 50 gm of absolute ethanol and allowed to solubilise in a closed vessel to give an optically clear solution. This was achieved by stirring the mixture at room temperature. The absence of crystalline material was confirmed by passing the material through a 200 nm pore size Cyclopore filter and examining the filter for crystals of the drug.

Ethanol was then removed from the resulting solution to give an intimate mixture of the CyA and the bilayer lipids. Ethanol removal was under moderate heating and vacuum assisted until gravimetric estimation revealed less than 1% of ethanol. The resultant lipid/CyA composition was a soft wax-like gel and contained 100 mg of drug in 1000 mg of sample. It was filled into soft capsules containing 100 mg of CyA in each capsule.

Example 2

A mixture of 100 g PC, lyso-PC and CyA in the molar ratios 28:2:1 was dissolved in 75 g of ethanol in a closed container to obtain a homogenous solution, as in Example 1. The resultant lipid composition following removal of the ethanol was a viscous paste. A small quantity of glycerol was mixed in with the paste-like material and worked in, to turn it into a less viscous gel. This CyA lipid composition was filled into soft gelatine capsules. Each capsule contained 50 mg of CyA in association with the lipid.

Example 3

A mixture of 100g of PC, lyso-PC and CyA in the molar ratios 5:5:1 was dissolved in 100g of ethanol in a closed container as described in example 1. The resultant lipid composition following removal of the ethanol was a soft wax. A small quantity of triglyceride (miglyol) was blended into the composition to lower its viscosity and facilitate filling into soft gelatine capsules. In practice, it was often found to be more convenient to add excipients of this type to the ethanolic solution of the components prior to solvent removal.

Example 4

A composition containing 100g PC, phosphatidylethanolamine, phosphatidyl inositol, lyso-PC, and CyA in the molar ratios 10:7:3.5:1:1 was dissolved in 75 g of ethanol under gentle heat, with stirring, as in Example 1 until no crystals of CyA could be detected. The ethanol was removed under vacuum until a clear gel was obtained. The resultant CyA lipid mixture obtained contained >5% ethanol. This was filled into soft capsules each containing 50 mg CyA.

Dispersion Tests

500 mg of the CyA lipid composition containing 50 mg of CyA was added to a beaker containing 20 ml of water adjusted to pH 8. Moderate stirring and agitation was carried out until it completely dispersed into lipid aggregates. A 10 ml aliquot of the the dispersion was passed through a 200 nm Cyclopore filter. No, or very few, crystals were seen on the filter in any of the above examples.

An aliquot of the dispersion was freeze-fractured and examined under an electron microscope (Fig 1). The

particles were observed to be vesicular and the mean diameter was estimated to be around 100nm. In Figure 1 the solid bar represents 100nm, and the micrograph shows lipid/cyclosporin complex dispersed in water, 40mg of lipid per ml.

Bioavailability

CyA lipid formulations as described above are expected to be bioequivalent to Sandimmune Neoral, without having to rely on potentially harmful surfactants with detergent properties. Advantageously, they make use of natural lipid components to carry and deliver therapeutic concentrations of an oil-soluble drug, predictably and effectively. The invention can provide a carrier of compounds that are poorly-water soluble and should, therefore, have wide-ranging pharmaceutical and other applications.

CLAIMS

1. A substantially homogenous composition for human administration comprising a biologically active lipophilic compound dissolved in or associated with at least one micelle-forming lipid.

2. The composition of claim 1, wherein the micelle-forming lipid is a monoacyl derivative of a phospholipid, glycolipid or spinglolipid.

3. The composition of claim 1 or 2, further comprising at least one bilayer-forming lipid.

4. The composition of claim 3, wherein the molar ratio of bilayer forming lipid to micelle forming lipid is 1:1 to 25:1.

5. The composition of claim 3 or 4, wherein the bilayer forming lipid is a phospholipid.

6. The composition of claim 3 or 4, wherein the bilayer forming lipid is phosphatidylcholine, phosphatidyl ethanolamine, phosphatidylglycerol, phosphatidylinisitol, phosphatidylserine or sphingomyelin.

7. The composition of claim 3 or 4, wherein the micelle

forming lipid and the bilayer forming lipid are in a mixture resulting from deacylation of a phospholipid.

8. The composition of claim 7, wherein the phospholipid is lecithin.

9. The composition of any preceding claim, wherein the the biologically active compound is a hydrophobic neutral cyclic peptide.

10. The composition of claim 9, wherein the biologically active compound is a fungal metabolyte.

11. The composition of any of claims 1 to 8, wherein the biologically active compound is a Cyclosporin.

12. The composition of any of claims 1 to 8, wherein the biologically active compound is Cyclosporin A.

13. The composition of any of claims 1 to 8, wherein the biologically active compound is a lipid soluble anti-infective or hormone compound.

14. A method for making a pharmaceutical composition for human oral administration which comprises:

dissolving a mixture of a phospholipid and at least

one other lipid material which forms small liposomes or mixed micelles in ethanol;

adding to the ethanol solution a lipophilic pharmaceutical to be associated therewith;

removing the ethanol; and

formulating the resulting composition as a unit dosage form.

15. The method of claim 14, wherein the lipophilic pharmaceutical is a cyclic fungal metabolite.

16. The method of claim 14, wherein the lipophilic pharmaceutical is cyclosporin A.

17. The method of any preceding claim, wherein the lipid mixture comprises a phospholipid and a lysolipid.

18. A composition for human oral therapy substantially as described in any of the examples.

The Patent Office

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Application No:	GB 9713140.3	**Examiner:**	Dr J Houlihan
Claims searched:	1-18	**Date of search:**	17 September 1997

Patents Act 1977
Search Report under Section 17

Databases searched:

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

UK Cl (Ed.O): A5B (BJB, BJC, BLB)

Int Cl (Ed.6): A61K 9/10, 9/107, 47/44

Other: ONLINE: WPI

Documents considered to be relevant:

Category	Identity of document and relevant passage		Relevant to claims
X	GB 2257359 A	(SANDOZ LTD.) page 21 Compositions X and I	1 & 10-12 at least
X	GB 2018712 A	(LITTLE A D INC.) column 3 lines 50-60; column 42 lines 28-39; Examples 1, 3-5, 16 & 18; page 15 lines 52-55	1, 2-6 & 13 at least
X	EP 0760237 A1	(CIPLA LTD.) Examples 1-9	1 & 2-12 at least
X	EP 0712631 A2	(BIOGAL GYOGYSZERGYAR RT) page 3 lines 22-32; Examples 1, 3-10	1 & 10-12 at least
X	EP 0700678 A1	(WAKAMOTO PHARM. CO.) Examples, especially 1, 15 and 19	1, 2-6, 10-14 & 16 at least
X	EP 0429248 A2	(SHISEIDO CO.) Example 5	1, 2-8 & 10-12 at least
X	EP 0282405 A2	(THE LIPOSOME CO.) column 4 lines 52-59; column 7 lines 20-27; Examples 2, 3, 5, 7 & 9	1, 2-6 & 13 at least

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
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The Patent Office

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Claims searched: 1-18

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Category	Identity of document and relevant passage		Relevant to claims
X	WO 88/06438 A1	(THE LIPOSOME CO.) Example 1	1, 2-6 & 12 at least
X	US 5529785	(DIETL H) Examples 1-7	1, 2-8 & 12 at least
X	US 4158707	(STEFFEN H & SCHMIDT D) Examples 1-12	1, 2-6 & 14 at least

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